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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,936	08/16/1999	HERMANN OPPERMANN	STK-077	4340
21323	7590	01/02/2004	EXAMINER	
TESTA, HURWITZ & THIBEAULT, LLP HIGH STREET TOWER 125 HIGH STREET BOSTON, MA 02110			SEHARASEYON, JEGATHEESAN	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/374,936

Applicant(s)

OPPERMANN ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/08/2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5 and 6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5 and 6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This office action is in response to the amendment and reply filed on 10/08/2003.

Claims 1-3, 5 and 6 are pending.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103, maintained.

3. The rejection of claims 1-3, 5 and 6 under 35 U.S.C. 103 (a) as being unpatentable over Keck et al. (a12) in view of Griffith (v120, Luyten (n12), Qian (u12), Daopin et al. (w12) is maintained. Applicant's arguments filed on 10/08/03 have been fully considered but are not persuasive. Applicants argue that the references either alone or in combination do not render the claims obvious over Keck in view of Griffith, Luyten, Qian or Daopin. This is not found to be persuasive for reasons of record in Paper No: 12, 16 and 26. Applicant alleges that the Office using an "obvious to try" rationale to make the chimeric molecule (see page 9 of the response). It is noted that all 35 USC § 103 rejections are based on the obvious to try rationale with a motivation for success to allow one of skilled in the art to make the invention. In addition, the art of record also provides evidence of generating chimeric TGF- β . In this case, Applicants are misconstructing the issue. It is certain that the molecules can be made; "obvious to try" is not an issue. Furthermore, Applicant has not provided any arguments of facts to indicate that the combination of references lacks the expectation for success.

Applicant asserts that the teachings of Keck et al. would lead one of skilled in the art to believe that the linker sequences are important to maintain proper confirmation and orientation and thus, proper biological activity, as indicated previously in Paper No: 16 (page: 5) and Paper No: 26 (page: 3). one cannot show non obviousness by attacking references individually where the rejections are based on combination of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). It is the combined teachings of the references that would have suggested to those of ordinary skill in the art. Contrary to Applicant's allegation that Keck et al. does not teach or suggest that the finger 1, heel and finger 2 domains of different members of the TGF- β super family may be swapped, Keck et al (U. S. Patent No: 6, 040, 431) does indeed teach that the "sequences for the finger and heel regions may be copied from respective finger and heel region sequences of any known TGF- β super family member identified herein" (column 4, lines 58-61). In addition, it also teaches the finger and heel regions may be selected from the amino acid sequence of a new member of this super family discovered here after (column 4, lines 61-63).

Furthermore, Applicant asserts that Qian et al. does not provide the motivation to make a chimeric molecule as claimed in the instant application (see page 11 of the specification. As indicated previously, Qian provides a reasonable expectation of success and a motivation to select CDMP- 2 domains for the chimera because CDMP-2 has chondrogenic activity *in vivo* but without substantially no osteogenic activity and an OP-1/CDMP-2 chimera would provide a practical approach to investigate

structure/function relationship (Paper No: 16, page 5). Applicant argues against Qian reference individually, one cannot show non obviousness by attacking references individually where the rejections are based on combination of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). It is the combined teachings of the references that would have suggested to those of ordinary skill in the art. In addition, Applicant alleges that Qian reference does not provide a reasonable expectation of success and motivation to select CDMP-2 domains for the chimera, arguing that Qian teaches just the opposite when it states that "one could not be certain that a chimeric TGF- β would fold correctly". This is mischaracterization of the reference. In fact Qian states that, "Although one could not be certain that a chimeric TGF- β would fold correctly, this approach has been successful in understanding the structure of other dimeric, disulfide-linked molecules, such as platelet-derive growth factor". The reference further states that, "Because this approach produces a recombinant protein of the same size as the endogenous molecule, it was likely that the chimeric TGF- β would maintain biological activity" (page 6294, 4th paragraph). Therefore, the motivation and reasonable expectation of success is clearly present. Further, absolute certainty is not the standard. Rather, all that is required to establish a *prima facie* case under USC 103 is a reasonable expectation of success

Applicant alleges that Daponin reference does not teach or suggest a chimeric molecule having a CDMP-2 finger 2 subdomain and a heel and finger 1 subdomain from a second member of the TGF- β super family of the present invention

that is biologically active. Applicant as indicated previously is attacking the references individually. It should also be noted that the claims of the instant invention does not require that the chimeric molecule be biologically active. Daponin reference was included in the rejection to indicate the close structural similarity between TGF- β 2 and other members of the TGF- β super family (Daponin et al., Table 2) and to suggest that that the only stable form of TGF- β 2 in solution is a dimer. Keck identifies the finger 1, heel and finger 2 regions and teaches making chimeric monomers that are chimeras of the finger 1, heel, and finger 2 regions. Therefore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a dimer because of the close structural similarity between TGF- β 2 and other members of TGF- β superfamily and the only stable form of TGF- β 2 is a dimer. Applicant acknowledges that Luyten reference discloses the sequence of CDMP-1 and CDMP-2. However, it is alleged that there is no teachings to suggest the chimeric molecules of the instant invention, again attacking the reference individually. Luyten reference was specifically included to teach the sequence of CDMP-1 and CDMP-2.

It is also alleged that Griffith does not disclose a chimeric molecule having a CDMP-2 finger 2 subdomain and a heel and finger 1 subdomain from a second member of the TGF- β super family. Again, Applicant is attacking the references individually. The Griffith disclosure was included, as indicated previously, to teach that all of the TGF- β superfamily members in Figure 6 share the OP-1/ TGF- β 2 structural motif (page 882, right column, full paragraph 1). The finger 2 domain of Op-1 comprises amino acid residues 105 to 139 (Figure 3). Amino acid residues 105 to 139 of Op-1 comprise the

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first amino acid residue after the third from the last Cys to the C-terminus of the molecule (figures 1 and 3).

Therefore, contrary to Applicants assertion that there are no teachings or suggestions to combine the references to teach the chimeric molecule claimed in the instant invention, there is exists the motivation and reasonable expectation of success to combine the teachings of Keck et al. (a12) in view of Griffith (v120, Luyten (n12), Qian (u12), Daopin et al. (w12) to generate the chimeric protein of the instant invention.

4. No claims are allowable over prior art.

5.THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Contact Information.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS



LORRAINE SPECTOR
PRIMARY EXAMINER